

Original Paper

The Efficacy of Fimasartan for Cardiovascular Events and Metabolic Syndrome (K-MetS Study): Rationale, Design and Participant Characteristics

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Key Words

Fimasartan · Hypertension · Angiotensin receptor blocker · Metabolic syndrome · Home blood pressure

Abstract

Fimasartan, the eighth angiotensin receptor blocker, was launched in March 2011 and was found to have an excellent efficacy and safety profile in a large cross-sectional population study [Safety and Efficacy of Fimasartan in Patients with Arterial Hypertension (Safe-KanArb); Park et al.: *Am J Cardiovasc Drugs* 2013;13:47–56]. However, there is no long-term study to evaluate its efficacy for major adverse cardiovascular events (MACE) and other effects. The purpose of this study (K-MetS study) was to evaluate whether the early reduction of blood pressure (BP) and/or correction of metabolic derangements with fimasartan will affect MACE and the development of diabetes after long-term use in patients with hypertension. A total of 10,734 patients were screened between October 2011 and October 2012. Of these, 10,601 patients from 582 private clinics and 11 university hospitals were enrolled and are currently treated with fimasartan. The primary endpoints are MACE (cardiovascular mortality, stroke, myocardial infarction, and hospitalization for heart failure) and the development of diabetes after 3 years of follow-up. In addition to BP monitoring in the clinic, home BP monitoring is

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performed in about two thirds of patients. The patients were 56.2 ± 10.9 years old (mean \pm SD), with 48.4% being women. The mean clinic and home systolic/diastolic BP at baseline were $145.0 \pm 17.0/88.8 \pm 11.4$ and $138.6 \pm 14.8/82.6 \pm 9.9$ mm Hg, respectively. The metabolic syndrome was found in 56.4%, increased abdominal circumference in 52.8%, elevated fasting glucose in 46.8%, hypertriglyceridemia in 44.7%, and low high-density lipoprotein cholesterol in 33.3% of patients. Further, complicated hypertension with diabetes occurred in 15.1%, ischemic heart disease in 3.3%, stroke in 0.9%, heart failure in 0.7%, and atrial fibrillation in 0.4% of patients. Most participants in this study had a low-to-moderate risk for hypertension. The K-MetS study is expected to provide valuable information about the effects of early BP control and correction of metabolic abnormalities on future cardiovascular outcomes relative to low-risk hypertension.

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Introduction

According to the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, early reduction of blood pressure (BP) in hypertensive patients at high cardiovascular (CV) risk may account for better CV outcomes irrespective of the treatment drug, which was either the calcium channel blocker (CCB) amlodipine or the angiotensin receptor blocker (ARB) valsartan [1]. As these medications achieved the same level of BP control, there is still no answer to the question as to which drug (CCBs or ARBs) would be superior in reducing CV events [2]. Previous large-scale studies have shown that renin-angiotensin blockers effectively suppress the risk for diabetes and prediabetic conditions (e.g., the metabolic syndrome) [3]. These suppressing effects on diabetes would prevent the risk for CV disease [4]. Aside from reducing BP, ARBs improve antioxidative stress, anti-inflammatory activity, endothelial function, and arterial remodeling [5]. These effects may prevent the development or aggravation of diabetes and abnormal metabolic disorders in hypertensive patients. Among ARBs, telmisartan or irbesartan may improve metabolic disorders through activating the peroxisome proliferator-activated receptor- γ [5–7]. However, there is still insufficient evidence to determine the effect of metabolic risk (or metabolic syndrome) on BP and to determine which metabolic component is more related to the incidence of the metabolic syndrome or which elements are more dangerous. Moreover, the implication of the reduction or prevention of these metabolic risks for the prevention of future CV events remains obscure.

Fimasartan (Boryung Pharmaceutical Company, Seoul, Korea) is the eighth ARB in the world. This newly developed antihypertensive shows a fast-acting effect in contrast to the slow-acting effects of previous ARBs which have been pointed out as a disadvantage [8]. In addition, fimasartan has long-term beneficial effects on lowering BP covering a full 24-hour period. Furthermore, its efficacy and safety have already been demonstrated in phase I, II, and III clinical trials as well as in a 24-hour ambulatory BP study [9]. The Safety and Efficacy of Fimasartan in Patients with Arterial Hypertension (Safe-KanArb) study is a recent retrospective study that has also shown excellent efficacy and safety of fimasartan in a large cohort of hypertensive patients in primary care clinics [10]. Still, a large-scale prospective study is required to verify the efficacy and safety of fimasartan for long-term outcomes in real-world clinical settings.

The aims of this study are to elucidate (1) the early effects of fimasartan on BP reduction, (2) the effects of a correction of the metabolic syndrome on the incidence of diabetes, CV events, and mortality after 3 years, and (3) the effects of fimasartan on the relation between the metabolic syndrome, diabetes, and CV events in hypertensive patients at low-to-moderate CV risk.

Methods

This is a prospective, multicenter, single-arm, observational study designed to enroll approximately 10,440 hypertensive patients treated with fimasartan on an open-label basis throughout Korea. All participants will be followed for at least 3 years. This study was approved by the Institutional Review Board Committee at the Cheil General Hospital, Kwandong University College of Medicine, on behalf of 582 primary care clinics. Another 10 university hospitals in Korea approved this study through their own institutional review board committees. Informed consent was obtained from all patients.

Study Subjects

In total, 10,601 hypertensive patients from 582 primary clinics and 11 university hospitals were enrolled between October 17, 2011 and October 31, 2012. To be included in the study, patients were required to (1) have hypertension, be at least 20 years of age, and intend to use fimasartan, (2) agree to participate in the study and sign the informed consent form, and (3) be in a fasting state at each visit. Patients who were treated with fimasartan at baseline were excluded. This pharmacoepidemiologic study was designed to reflect real-world clinical settings.

Endpoint and Outcome Evaluation

The primary endpoint is the first incidence of a major adverse cardiovascular event (MACE), such as CV death, nonfatal stroke, nonfatal myocardial infarction, and hospitalization for heart failure. Secondary endpoints are: (1) changes in metabolic risk after 3 months; (2) new onset of the metabolic syndrome and diabetes after 1 and 3 years of follow-up; (3) changes in BP and the relation of adverse events depending on the presence of the metabolic syndrome after 3 months and 1 year of follow-up; (4) early effects of the correction of the metabolic risk and metabolic syndrome on MACE in the short- and long-term follow-up; (5) changes in home BP and the difference between home BP and clinic BP; (6) changes in the incidence of white coat and masked hypertension measured by home BP readings; (7) changes in BP variability, and (8) effects of fimasartan on sodium intake and the incidence of MACE. All endpoints and clinical outcomes are evaluated by the endpoint evaluation committee of this study, including blood chemistry and other laboratory examinations. All electrocardiographic findings are interpreted by a cardiologist in a core laboratory of the Cheil General Hospital.

BP Measurements

Clinic BP measurements were done under standardized conditions (in the same arm by the same physician or nurse with the same equipment). The Omron HEM-7220 was used at the clinic and the Omron HEM-7200 (both Omron, Tokyo, Japan) was used at home [11]. These are upper arm cuff devices based on the cuff oscillometric principle. Home BP measurements were taken twice in the morning and evening, and the average of two or more BP readings within a 2-min interval from the same arm on each occasion was recorded for 7 consecutive days. The morning BP was measured within 1 h of awakening, after urination, in a sitting position, after resting for 5 min, and before taking medications or eating. In the evening, the BP was measured before going to bed, after resting for 5 min, and in a sitting position. An average of 4 or more daily recordings was used for the analysis after those from the first day.

Definition of the Metabolic Syndrome

In this study, the harmonized definition for the metabolic syndrome is used: (1) BP \geq 130/85 mm Hg or taking medications; (2) blood glucose level \geq 100 mg/ml or taking medications; (3) waist circumference \geq 90 cm for men and \geq 80 cm for women, following Asian-specific cutoffs; (4) high-density lipoprotein cholesterol (HDL-C) $<$ 40 mg/dl for men and $<$ 50 mg/dl for women or taking medications, and (5) triglyceride \geq 150 mg/dl or taking medications [12, 13]. The metabolic syndrome was diagnosed if a subject had at least 3 of the 5 above-mentioned criteria. For the measurement of the waist circumference, the patients were asked to stand with their feet together and breathe out gently, with the measurement then taken at the midpoint between the ribs and the iliac crest.

Laboratory Analysis

Central laboratory analyses (Green Cross Reference Lab, Korea) were performed in all clinics. Samples were taken after fasting for more than 8 h. Complete blood counts were performed with an automated hematology analyzer (Sysmex SE9000; Toa Medical Electronics, Kobe, Japan). Serum sodium and potassium

concentrations were analyzed via an indirect ion-specific electrode on a Roche Modular ISE 900 (Roche Diagnostics, Mannheim, Germany). Plasma levels of total cholesterol, triglycerides, HDL-C, and low-density lipoprotein cholesterol (LDL-C) were measured using the Dimension Clinical Chemistry System (Dade Behring Inc., Newark, Del., USA), Roche Elecsys 2010, and Modular Analytics E170 (Elecsys module) immunoassay analyzers (Roche Diagnostics).

Sample Size Estimation

The sample size was estimated based on the incidence of MACE, as this was the primary endpoint. The Health Insurance Review and Assessment Service reported that the incidence of MACE was 13.8% during an average 3-year follow-up period among incident hypertensive patients treated with antihypertensive drugs. Additionally, the incidence of MACE was estimated to be around 5–8% each year among patients with hypertension [14]. After assuming that the incidence of MACE is 5–8%, an effective size will be 8,874 patients to prove a difference falling into 7% of a relative risk reduction for an 80% power and a 5% significance level. Considering a 15% dropout rate, approximately 10,440 subjects are needed in this study. If the incidence required is expected to fall short of the primary evaluation criteria until the planned study end over the clinical study period, the number of subjects and follow-up period will be adjusted to maintain the power of the test.

Statistical Analysis

The baseline characteristics of the study subjects were compared between genders using the χ^2 test for dichotomous variables or the t test for continuous variables. The incidence of MACE and 95% confidence interval in the group receiving fimasartan will be estimated using the appropriate statistical method after 1 and 3 years of follow-up. Subgroup analyses will consist of several cohorts based on sociodemographic characteristics such as age, gender, weight, and comorbidities. Changes in metabolic risk (lipids, weight, BP, and insulin resistance) after 3 months or 1 year of follow-up will be examined using a paired t test or mixed regression model among subgroups. The χ^2 test or Fisher's exact test will be used to analyze the effect of early metabolic risks on MACE, and the Cox proportional hazard model (or appropriate survival analysis) will be used to control for potential confounders. Differences between measured variables (e.g., BP) will be examined using a two-way analysis of variance or mixed regression model among the subgroups after 3 months and 1 year of follow-up. For the evaluation of secondary effectiveness, we will carry out two interim analyses to conduct secondary research at 3 months and 1 year of follow-up. All analyses will be performed using SAS 9.3 (SAS Institute, Cary, N.C., USA).

Results

In total, 10,734 patients were screened at 605 institutions by 605 investigators. Of these, 10,601 were enrolled in this study after excluding 133 patients because they withdrew their consent. The baseline characteristics of the 10,601 enrolled patients are summarized in table 1. Patients' concomitant diseases, indications for fimasartan use, and medical history are also described in table 1.

The prevalence of hyperlipidemia, diabetes mellitus, CV disease, cerebrovascular disease, and electrocardiographic abnormalities at baseline was 49.6, 15.1, 3.3, 0.9, and 17.0%, respectively. Subjects taking antidiabetic agents or lipid-lowering drugs were defined as having diabetes or hyperlipidemia, respectively. The distribution of age was similar between men (51.6%) and women (48.4%). The mean (\pm SD) clinic systolic/diastolic BP (SBP/DBP) in both men and women was $145.0 \pm 17.0/88.8 \pm 11.4$ mm Hg, whereby SBP/DBP was significantly higher in men than in women ($p = 0.011$ and $p < 0.001$ for SBP and DBP, respectively). The home SBP/DBP was $138.6 \pm 14.8/82.6 \pm 9.9$ mm Hg, and BP in men was significantly higher than in women (both $p < 0.001$ for SBP and DBP; table 2). Clinic BP was strongly correlated with home BP. The correlation coefficients between home and clinic BP was $R^2 = 0.38$ for SBP and $R^2 = 0.35$ for DBP (fig. 1).

Table 1. Patient characteristics at baseline

	All (n = 10,601)	Men (n = 5,474)	Women (n = 5,127)	p value
Age, years	56.2±10.9	54.8±11.1	57.6±10.4	<0.001
Height, cm	163.0±8.6	169.2±6.1	156.4±5.6	<0.001
Weight, kg	67.0±11.4	72.7±10.4	61.0±9.1	<0.001
Body mass index	25.1±3.2	25.3±3.0	24.9±3.4	<0.001
Current smoking, %	17.1	30.6	2.6	0.034
FHx of CV disease, %	15.8	15.2	16.5	0.058
Hypertension history, years	3.2±4.7	3.2±4.7	3.2±4.7	0.899
Concomitant disease				
Diabetes	1,602 (15.1)	919 (16.8)	683 (13.3)	<0.001
Ischemic heart disease	351 (3.3)	197 (3.6)	154 (3.0)	0.087
Stroke	100 (0.9)	54 (1.0)	46 (0.9)	0.635
Indication				
Naive	4,712 (45.3)	2,461 (45.7)	2,251 (44.8)	0.003
Add-on	3,715 (35.7)	1,846 (34.3)	1,869 (37.2)	
Switch	1,986 (19.1)	1,077 (20.0)	909 (18.1)	
Medication history				
Diabetes	1,298 (12.2)	748 (13.7)	550 (10.7)	<0.001
CV disease	198 (1.9)	101 (1.9)	97 (1.9)	0.859
Dyslipidemia	1,887 (17.8)	920 (16.8)	967 (18.9)	0.006
Hypertension	5,052 (47.7)	2,621 (47.9)	2,431 (47.4)	0.369

Values represent mean ± SD or n (%), unless otherwise indicated. FHx = Family history.
p value: men vs. women.

Table 2. Clinic and home BP at baseline

	All (n = 10,601)	Men (n = 5,474)	Women (n = 5,127)	p value
Clinic BP				
SBP, mm Hg	145.0±17.0	145.4±16.4	144.5±17.5	0.011
DBP, mm Hg	88.8±11.4	89.7±11.5	87.9±11.1	<0.001
PR, beats/min	74.1±10.0	74.5±10.3	73.6±9.7	<0.001
Home BP				
SBP, mm Hg	138.6±14.8	139.5±13.9	137.7±15.6	<0.001
DBP, mm Hg	82.6±9.9	83.8±9.9	81.4±9.7	<0.001
PR, beats/min	72.5±8.8	73.2±9.3	71.8±8.1	<0.001

Values represent mean ± SD. PR = Pulse rate. p value: men vs. women.

Men had significantly higher levels of fasting glucose, triglycerides, and waist circumference compared with women. On the contrary, women had a greater serum total cholesterol, and HDL-C compared with men (table 3). The prevalence of the metabolic syndrome was significantly higher in women (57.9%) than in men (55.0%; $p = 0.003$). Except for a high BP, the highest values among the metabolic components were reached for triglycerides (51.4%) in men and for waist circumference (64.4%) in women (table 4). Table 5 shows the number of metabolic risk factors between men and women and demonstrates a higher prevalence of several risk factors for women compared with men.

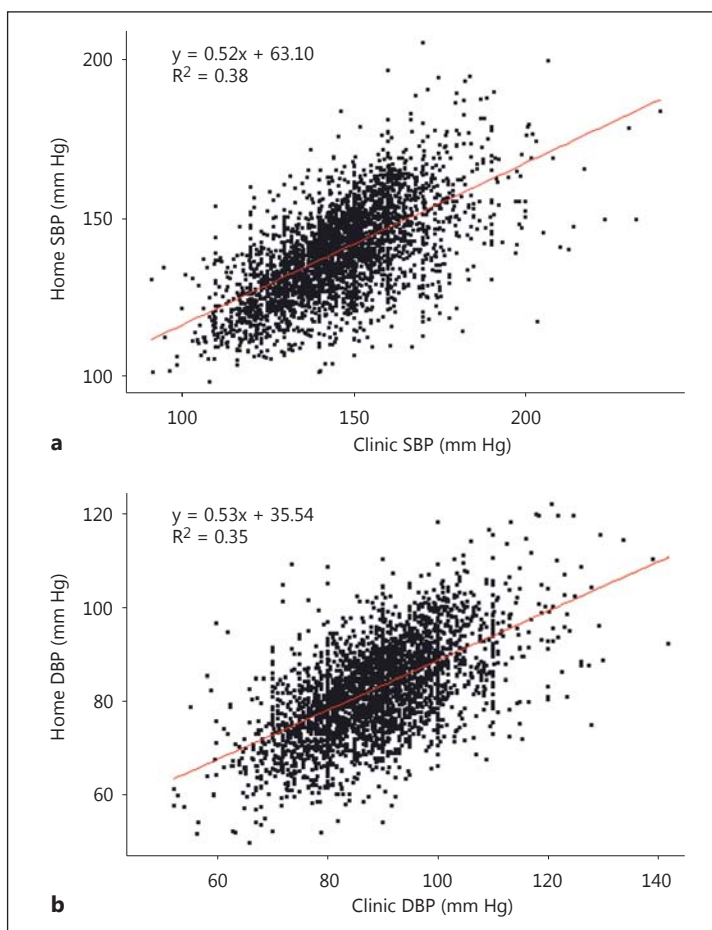


Fig. 1. Scatter diagrams of clinic and home BP at baseline ($n = 10,601$). Each patient's clinic and home BP was plotted for SBP (**a**) and DBP (**b**) with regression equations.

Table 3. Metabolic risk factors at baseline

Metabolic risk factor	All ($n = 10,601$)	Men ($n = 5,474$)	Women ($n = 5,127$)	p value
Waist circumference, cm	85.7 ± 9.2	88.4 ± 8.3	82.9 ± 9.3	<0.001
Fasting blood sugar, mg/dl	108.6 ± 39.9	111.9 ± 42.2	105.1 ± 36.9	<0.001
Total cholesterol, mg/dl	194.5 ± 38.3	190.8 ± 37.8	198.6 ± 38.3	<0.001
Triglyceride, mg/dl	167.8 ± 111.2	184.9 ± 124.1	149.5 ± 92.1	<0.001
HDL-C, mg/dl	51.7 ± 14.3	48.7 ± 13.3	54.9 ± 14.7	<0.001

Values represent mean \pm SD. p value: men vs. women.

Discussion

The K-MetS study is a large, nationwide, multicenter, prospective observational study and gives important pharmacoepidemiologic information on hypertension in Korea. Previously, we have performed a retrospective observational study in primary care clinics to represent a real-world clinical setting [10]. This is a prospective extension of that study and includes relatively young subjects and subjects with mild-to-moderate hypertension. The

Table 4. Percentage and components of the metabolic syndrome at baseline

	All (n = 9,335)	Men (n = 4,828)	Women (n = 4,507)	p value
Metabolic syndrome	5,264 (56.4)	2,635 (55.0)	2,609 (57.9)	0.005
High waist circumference	4,927 (52.8)	2,026 (42.0)	2,901 (64.4)	<0.001
High BP factor	9,335 (100)	4,828 (100)	4,507 (100)	–
High fasting glucose	4,370 (46.8)	2,471 (51.2)	1,899 (42.1)	<0.001
Low HDL-C	3,108 (33.3)	1,313 (27.2)	1,795 (39.8)	<0.001
High triglyceride	4,173 (44.7)	2,483 (51.4)	1,690 (37.5)	<0.001

Values represent n (%). p value: men vs. women.

Table 5. Risk factors for the metabolic syndrome

	All (n = 9,335)	Men (n = 4,828)	Women (n = 4,507)	p value
One risk factor	1,388 (14.9)	767 (15.9)	621 (13.8)	0.004
Two risk factors	2,683 (28.7)	1,406 (29.1)	1,277 (28.3)	0.401
Three risk factors	2,628 (28.2)	1,390 (28.8)	1,238 (27.5)	0.156
Four risk factors	1,905 (20.4)	953 (19.7)	952 (21.1)	0.097
Five risk factors	731 (7.8)	312 (6.5)	419 (9.3)	<0.001

Values represent n (% of all). p value: men vs. women.

study was designed to recruit subjects from all over Korea from primary care clinics to tertiary university hospitals in order to reflect practical daily clinical practice in Korea.

In the 2011 Fifth Korea National Health and Nutrition Examination Survey (KNHANES V-2), hypertension was present in 26.5% and diabetes in 9% of a representative sample of the Korean population [15]. The frequency of diabetes in our study was 15.1% because of a high prevalence of obese and elderly subjects. Thus, our patients may also represent a relatively higher risk for CV disease compared with the general population. However, this study is similar to previous studies conducted in primary care clinics in Korea (Safe-KanArb) and Japan [Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH)] [10, 16], with relatively more mild-to-moderate risk subjects than in most clinical trials on hypertension [4, 17, 18]. Another advantage is that this study involves 11 university hospitals, so that high-risk populations were also included. In Korea, most incident hypertensive patients or hypertensive patients without comorbidities usually visit primary care clinics due to coverage by the health insurance program. On the contrary, medical utilization of tertiary hospitals (e.g., university hospitals) is covered by the health insurance program for cases of hypertension with comorbidities. Thus, the advantage of this cohort as a whole is the inclusion of a mild-to-moderate risk population from primary or secondary care clinics as well as a higher-risk population from tertiary university hospitals, reflecting realistic circumstances throughout the country with regard to hypertension.

The baseline prevalence of the metabolic syndrome in our study is 56.4%, which is higher than that reported by either KNHANES (31.3%) or the Atherosclerosis Risk of Rural Areas in Korea General Population (ARIRANG) rural cohort study (38.1%) [19]. Over the past 10 years, the prevalence of the metabolic syndrome increased progressively from 24.9 to 31.3% as a

consequence of greater rates of dyslipidemia and abdominal obesity. The incidence of the metabolic syndrome also increased rapidly by 18.4% in men and 16.4% in women during a mean of 2.6 years in the ARIRANG cohort, which was especially notable when hypertension was present [19]. Collectively, Korea seems to have experienced a rapid increase in the prevalence and incidence of the metabolic syndrome during the 2000s, partly due to an increasing adoption of Western lifestyle patterns [20]. Therefore, our study may reflect a period of rapid increase in the frequency of this syndrome, which can be translated to the increased frequency of CV diseases in Korea.

Despite the high prevalence of the metabolic syndrome in Korea and other countries, there is a paucity of data to demonstrate the clinical implications of this syndrome in patients with hypertension or the reduction of metabolic risks for MACE in these patients. Thus, our study gives a clue to the unsolved issue regarding the association of the metabolic syndrome in hypertension with future CV outcomes. From our study, it is possible to make a predictive model of CV events in realistic patient settings.

More specifically, our study reflects the real-world clinical setting because of the patients' risk diversity considering that most hypertensive patients with low or moderate risk are managed in primary care clinics. This may also be true given that patients in tertiary university hospitals usually have a relatively high CV risk. The risk distribution in our study also makes it possible to analyze the implications of the metabolic syndrome in hypertension differently in low-to-moderate- versus high-risk patients, in addition to analyzing the preventative effects on future CV outcomes. Upon further analysis of the VALUE study, ARB monotherapy resulted in better outcomes for heart failure and new-onset diabetes compared with CCB monotherapy [21]. Notably, patients undergoing monotherapy were at a relatively lower risk than the main VALUE population; nonetheless, these patients were still at a higher risk than our population because of their older age (mean age of 67 years) and a 30% frequency of diabetes. Therefore, the K-MetS study will show the effects of early BP reduction in a more realistic clinical practice setting. The study will also show the effects of fimasartan, a new ARB, on the presence or absence of the metabolic syndrome on a naive, switch, or add-on basis.

Another unresolved issue is the effect of early BP reduction on CV outcomes in hypertensive patients. Prompt BP control in the VALUE study demonstrated a difference in CV outcomes regardless of the treatment regimen (either CCB- or ARB-based therapy) [1]. As the study population in the VALUE trial represented high-risk patients, the population characteristics in the K-MetS study are different. Thus, our study may suggest an important clue regarding the effects of early BP reduction on future CV outcomes in a low-risk population.

In conclusion, in the K-MetS study, subjects were enrolled from 582 primary and secondary care clinics and 11 university hospitals between October 2011 and October 2012. This study was designed to represent a real-world clinical practice setting and to investigate the actual meaning of the metabolic syndrome in patients with hypertension, the effects of early BP reduction in relatively mild-to-moderate hypertension, and both the therapeutic and side effects of fimasartan-based treatment in the presence or absence of the metabolic syndrome. This study will provide new insights into the prevention of CV events in clinic and hospital patients with hypertension.

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